QnAs with Matthew V. Tirrell

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Matthew V. Tirrell has been at the forefront of efforts to understand and apply the surface and interfacial properties of organic polymers and micellar nanoparticles. His contributions to the field led to his election to the National Academy of Sciences in 2019. Now dean of the Pritzker School of Molecular Engineering at the University of Chicago and a senior scientist at the Argonne National Laboratory, Tirrell has unraveled phase separation in polymers and nanoparticles and helped design and synthesize novel self-assembling materials with targeting and therapeutic potential. In his Inaugural Article, Tirrell describes self-assembling micelle nanoparticles that can target atherosclerotic plaques and deliver packaged nucleic acids to the plaques as potential treatments (1).

PNAS: How did you first become interested in using nanoparticles to target atherosclerotic plaques?

Tirrell: More than a decade ago, when I was at the University of California, Santa Barbara, I made the acquaintance of a well-known scientist named Erkki Ruoslahti. He had been developing methods for phage-display discovery of targeting peptides, and we started focusing on this one peptide that homed in to blood clots. We published a couple of papers using the peptide that Erkki had discovered, placed into constructs we developed that at the time we called peptide amphiphiles. These were conjugate molecules, where a peptide is coupled to a hydrophobic tail with a polyethylene glycol spacer in between. The hydrophobic tails come together and make a well-defined spherical micelle with about a hundred molecules [and] a very high multivalent display of these targeting peptides on the outside of the micelle. We showed that a particle like this could be injected into the tail vein of a mouse and find pathological tissue that had blood clots on it. These tissues can be tumors, because tumors have leaky blood vessels, or they could be atherosclerotic plaques, because so-called vulnerable or unstable plaques that might be prone to rupture typically have microclots and microfractures on their surface.

PNAS: How did your Inaugural Article (1) come about, and what did you find?

Tirrell: We showed in 2009 that we could create nanoparticles that homed to atherosclerotic plaques (2). When I moved to the University of Chicago in 2011, I met Yun Fang, the principal coauthor on the Inaugural Article (1). During his postdoctoral work, he had done some early work discovering that microRNA-92a in endothelial cells is responsible for a proinflammatory response that leads to atherosclerosis. Meanwhile, our work had moved on from hydrophobically created micelles to polyelectrolyte complexation as a tool for self-assembly. It turns out you can make micelles with them, too. Yun knew that there was a commercially available inhibitor of microRNA-92a [that] is itself an oligonucleotide, so it's a nucleic acid that essentially binds to microRNA-92a and inhibits its action. We made polyethylene glycol-poly-L-lysine conjugates, poly-L-lysine being a cationic polymer that we knew complexes strongly with nucleic acids. Then, on the outside, instead of putting a peptide that targets blood clots, we put a peptide that targets inflamed endothelium. The marker for vascular inflammation that we used was the up-regulation of a cell-surface receptor called vascular cell adhesion molecule 1

Matthew V. Tirrell. Image credit: University of Chicago, Chicago, IL.

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(VCAM-1). So, we made these polyelectrolyte complex micelles carrying a payload of the microRNA-92a oligonucleotide inhibitor, and we found that it strongly slows narrowing of blood vessels and the growth of atherosclerotic plaques in a mouse model.

PNAS: What are the advantages of using the targeting nanoparticle micelles?

Tirrell: The microRNA-92a inhibitor is pretty effective if you just inject it naked, and it does reduce the growth of atherosclerotic plaques, but our method worked even better than just delivering the naked inhibitor. We believe that's because of targeting, including due to local delivery of the payload and conceivably because the engagement of our micelles with cell-surface receptors provides some assistance in getting into the cells. A nice thing about self-assembled micelles is that they're modular, so we could incorporate other kinds of functional peptides into the same construct if there was another receptor that we wanted to target simultaneously or there was something to increase the localization or the delivery. There are several avenues to further optimize the construct.

PNAS: What are some of the potential applications of this work?

Tirrell: We've been trying to pin down how general this microRNA is as a therapeutic target for other kinds of vascular remodeling, and whether our treatment would work in other places where this kind of vascular remodeling occurs, like in kidney dialysis patients. Vascular surgeons create what's called an arteriovenous fistula for kidney dialysis patients, which turns out to be a good way of accessing the blood vessels to connect an artery to a vein. It produces robust blood flow, but this kind of disturbed blood flow downstream of the fistula often causes the blood vessel to close off. Also, after angioplasty, when there's a coronary artery blockage and a stent is implanted, there's vascular remodeling there that sometimes closes off the blood vessel. So, this paper (1) has given us some insights not only into how to treat atherosclerosis, but other diseases related to remodeling of blood vessels. We're also thinking about other indications, such as using the same kind of construct for pulmonary fibrosis by using a targeting peptide that targets the construct to pathological lung tissue instead of cardiovascular tissue. I think there's some generality to this whole platform, and this paper has given us new ideas of other things we can do with the same construct.

PNAS: What are the therapeutic implications of these findings?

Tirrell: Even though more people die of cardiovascular disease than cancer, cardiovascular disease is still underserved by the nanomedicine community. And for a wide variety of reasons, these approaches might actually work better for cardiovascular disease than cancer. For instance, cardiovascular disease is localized, it's not metastatic, so it's not going to spread all over the body in the way that cancer does. I think this work starts to open up cardiovascular disease as a practical and scientifically interesting direction for nanomedicine.

1 Z. Zhou *et al.*, Targeted polyelectrolyte complex micelles treat vascular complications in vivo. *Proc. Natl. Acad. Sci. U.S.A.* **118**, e2114842118 (2021).

2 D. Peters *et al.*, Targeting atherosclerosis by using modular, multifunctional micelles. *Proc. Natl. Acad. Sci. U.S.A.* **106**, 9815–9819 (2009).

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